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 TITLE: Preparation of N-acyl-phenylalanine derivatives as
 inhibitors of α 4-mediated cell adhesion
 INVENTOR(S): Sircar, Ila; Gudmundsson, Kristjan S.; Martin, Richard
 PATENT ASSIGNEE(S): Tanabe Seiyaku Co., Ltd., Japan
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 LANGUAGE: English
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WO 9936393	A1	19990722	WO 1999-US993	19990119
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
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BR 9907040	A	20001017	BR 1999-7040	19990119
EP 1049662	A1	20001108	EP 1999-904115	19990119
EP 1049662	B1	20060621		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
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PRIORITY APPLN. INFO.:			US 1998-71840P	P 19980120
			JP 2000-540111	A3 19990119
			WO 1999-US993	W 19990119
			US 2000-619712	A3 20000719

OTHER SOURCE(S): MARPAT 131:116517
 GI For diagram(s), see printed CA Issue.

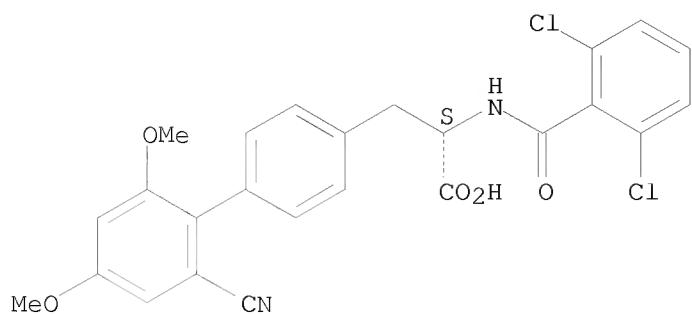
AB The present invention relates to a pharmaceutical composition comprising as an active ingredient a compound of formula [I; wherein ring A is an aromatic or a heterocyclic ring; Q is a bond, carbonyl, lower alkylene optionally substituted by HO or Ph, lower alkenylene, or -O-(lower alkylene)-; n is 0, 1 or 2; Z is oxygen or sulfur; W is oxygen, sulfur, -CH:CH-, -NH- or -N:CH-; R1, R2 and R3 are the same or different and are hydrogen, halogen, hydroxyl, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkoxy group, a substituted or unsubstituted amino group, CO₂H or an amide or an ester thereof, cyano, lower alkylthio, lower alkanesulfonyl, substituted or unsubstituted SO₂NH₂, etc.; R4 is tetrazolyl, carboxyl group, amide or ester; R5 is hydrogen, nitro, amino, hydroxyl, lower alkanoyl, lower alkyl, etc.; R6 is selected from (a) a substituted or unsubstituted Ph group, (b) a substituted or unsubstituted pyridyl group, (c) a substituted or unsubstituted thienyl group, (d) a substituted or unsubstituted benzofuranyl group, etc.; or a pharmaceutically acceptable salt thereof]. These phenylalanine derivs. are useful for treating or preventing conditions caused by α 4-mediated cell adhesion such as rheumatoid arthritis, asthma, psoriasis, eczema, contact dermatitis and other skin inflammatory diseases, diabetes, multiple sclerosis, systemic lupus erythematosus (SLE), inflammatory bowel disease including ulcerative colitis and Crohn's disease, and other diseases involving leukocyte infiltration of the gastrointestinal tract, or other epithelial lined tissues, such as skin, urinary tract, respiratory airway, and joint synovium.

N-(tert-butoxycarbonyl)-O-(trifluoromethanesulfonyl)-L-tyrosine Me ester (preparation given) was coupled with 2-methoxybenzene boronic acid in toluene/DMF in the presence of K₂CO₃ and Pd(PPh₃)₄ at 80 °C for 24 h to give N-(tert-butoxycarbonyl)-4-(2-methoxyphenyl)-L-phenylalanine Me ester. The latter compound was treated with CF₃CO₂H in CH₂Cl₂ for 1.5 h to remove the Boc group and then condensed with 2,6-dichlorobenzoyl chloride in the presence of diisopropylethylamine at room temperature for 24 h to give N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine Me ester (II) which was saponified with LiOH in THF/MeOH at room temperature for 3 h, evaporated, treated with H₂O, adjusted pH 2, and extracted with EtOAc to give N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (III). II and III in vitro inhibited at IC₅₀ of 1 \geq and 0.3 \geq μ M, resp., β 7-mediated cell adhesion which measured the adhesive interactions of a B-cell line, RPMI, known to express α 4 β 7, to the alternatively spliced region of fibronectin referred to as CS-1, in the presence of test compds.

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 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of N-acyl-phenylalanine derivs. as inhibitors of α 4-mediated cell adhesion for prevention and treatment of diseases caused by α 4-mediated cell adhesion)

RN 232272-83-2 CAPLUS
 CN [1,1'-Biphenyl]-4-propanoic acid, 2'-cyano- α -[(2,6-dichlorobenzoyl)amino]-4',6'-dimethoxy-, (α S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT:

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THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT